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### REMARKS

Reconsideration of the Final Office Action mailed June 23, 2005, (hereinafter "instant Office Action") and withdrawal of the rejection of claims 21-27, 32 and 33 are respectfully requested.

In the instant Office Action, claims 1-88 are listed as pending, claims 1-20, 28-31 and 34-88 are withdrawn from consideration and claims 21-27, 32 and 33 are listed as rejected.

The Examiner has maintained the rejection of claims 21-27, 32 and 33 under 35 U.S.C. §112, first paragraph, alleging that the specification, while being enabling for the atomic coordinates for residues 802-1124 of Tie-2 and Inhibitor III complex, does not reasonably provide enablement for the atomic coordinates of an unbound version of a Tie-2 polypeptide or atomic coordinates of the complete polypeptide of Tie-2 and Inhibitor III complex. The Examiner alleges that the invention as presently stated in claim 21 encompasses these additional sets of atomic coordinates, but that they are not included in the specification which consequently causes a lack of scope of enablement of the instant invention for one of ordinary skill in the art. Applicants respectfully traverse this rejection. Applicants maintain the arguments that were presented in the Reply mailed December 23, 2003, the Reply filed July 8, 2004, the Request for Continued Examination filed September 8, 2004, the Reply mailed April 7, 2005 and the Reply mailed October 24, 2005.

Applicants respectfully point out that claims 21-27, 32 and 33 are all method claims. Specifically the claims are directed to a method of identifying a compound which is an inhibitor of a Tie-2 protein. The Examiner has rejected these method claims because allegedly Applicants have not "provide enablement for the atomic coordinates of an unbound version of a Tie-2 polypeptide or atomic coordinates of the complete polypeptide of Tie-2 and Inhibitor III complex". However, none of the steps of the claimed method entail crystallizing a protein. Step (a) of the claimed method is obtaining the atomic coordinates of a crystal of a polypeptide. There is no claim to making the crystal. One could theoretically obtain the crystallized protein from another source. Nonetheless, Applicants have taught crystallization conditions for diphosphorylated Tie-2 802-1124 on page 48, Tie-2 (D964N) 802-1124 (SEQ ID NO 1) on page 49 and for Tie-2 (D964N) 802-11234 (SEQ ID NO 2) on page 51 of the instant application. Further, Table II on pages 53-56 lists crystallization conditions for Tie-2/inhibitor complexes. Applicants have provided the crystallization conditions such as protein concentration, buffer

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concentration, pH, buffer identity, precipitant and additive parameters to enable one of ordinary skill in the art to crystallize the protein. Applicants have enabled the steps of obtaining atomic coordinates, using atomic coordinates and identifying a compound which binds to one or more active subsites wherein the compound is an inhibitor of Tie-2. Therefore, Applicants have enabled claims 21-27, 32 and 33.

Based upon the foregoing, the rejection of claims 21-27, 32 and 33 under 35 U.S.C. §112, first paragraph, for lack of scope enablement is obviated and should be withdrawn.

The Examiner has maintained the rejection of Claims 21-27, 32 and 33 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the invention was filed, had possession of the claimed invention. The Examiner alleges that "due to the open claim language of 'comprises' in claim 21, this claim is directed to encompass amino acid sequences that do not meet the written description provision of 35 U.S.C. §112, first paragraph." Applicants respectfully traverse this rejection. Applicants maintain the arguments presented in the Reply mailed December 23, 2003, the Reply filed July 8, 2004, the Request for Continued Examination filed September 8, 2004, the Reply mailed April 7, 2005 and the Reply mailed October 24, 2005.

M.P.E.P. §2163 states:

'Comprising' is a term of art used in claim language which means that the named elements are essential but other elements may be added and still form a construct within the scope of the claim

With respect to the rejection of claim 27, as the Examiner pointed out, the term "comprising" is open claim language. In claim 27 "comprising" refers to the polypeptide containing at least (i.e. at a minimum) the catalytic domain of Tie-2. Whether it is the unbound Tie-2 polypeptide or the entire Tie-2 polypeptide and inhibitor III complex is being used is not relevant so long as the catalytic domain of Tie-2 is present.

The Examiner admits that Applicants have provided atomic coordinates for the catalytic domain of Tie-2 (residues 802-1124). Claim 21 is directed to a method of identifying a compound which is an inhibitor of Tie-2. Step (a) of claim 21 is to obtain the atomic coordinates of a crystal of a polypeptide comprising the catalytic domain of a Tie-2 protein. As Applicants describe at lines 21-25, page 3 of the instant specification:

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In another embodiment, the method for identifying a compound which inhibits the catalytic activity of Tie-2, comprises the step of determining the ability of one or more functional groups and/or moieties of the compound, **when present in, or bound to, the Tie-2 catalytic domain, to interact with one or more subsites of the Tie-2 catalytic domain.** (emphasis added)

Applicants respectfully point out that in order for a compound to inhibit a Tie-2 protein, one or more functional groups and/or moieties of the compound must be present in or bound to the Tie-2 catalytic domain. Thus, the catalytic domain of Tie-2 (residues 802-1124) must be present in order for a compound to inhibit the Tie-2 protein. Therefore, so long as the catalytic domain of Tie-2 is present, it does not matter whether it is the unbound Tie-2 polypeptide or the entire Tie-2 polypeptide and inhibitor III complex is being used. Only the catalytic domain of Tie-2 is essential for claim 21.

Based upon the foregoing, the rejection of Claims 21-27, 32 and 33 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of the invention was filed, had possession of the claimed invention, is obviated and should be withdrawn.

The Examiner has maintained the rejection of claims 21, 22 and 26 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen et al (P/N 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)). Applicants respectfully traverse this rejection and maintain the arguments presented in the Reply mailed December 23, 2003, the Reply filed July 8, 2004, the Request for Continued Examination filed September 8, 2004, the Reply mailed April 7, 2005 and the Reply mailed October 24, 2005.

In the Advisory Action mailed November 21, 2005 in response to Applicants' argument that the atomic coordinates of the crystal are functionally related to the method of claim 21 because the atomic coordinates identify the active subsites of Tie-2, which in turn allows one to identify or design an inhibitor of Tie-2, the Examiner states "...coordinates do not actively play a role which alters computer system functionality". Applicants respectfully disagree with the Examiner's assessment that the atomic coordinates are nonfunctional printed matter. Different polypeptides generate different atomic coordinates. One would not use a STAT protein to identify compounds which inhibit a Tie-2 protein because one would not obtain the correct

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atomic coordinates to bind in the catalytic domain of Tie-2. The identification of a compound to inhibit a Tie-2 protein is only possible by using the atomic coordinates generated by a polypeptide containing the catalytic domain of Tie-2. The atomic coordinates are not nonfunctional printed matter but instead allow one to assess the ability of a compound to inhibit the catalytic activity of Tie-2. Therefore they are an important aspect of the invention and not nonfunctional printed matter.

Based upon the foregoing, the rejection of claims 21, 22 and 26 under 35 U.S.C. §103(a) over Chen et al. in view of *In re Gulack* is obviated and should be withdrawn.

The Examiner has maintained the rejection of claims 21-27 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen et al (P/N 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)), *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) and Ziegler (P/N 5,447,860). Applicants respectfully traverse this rejection and maintain the arguments presented in the Reply mailed December 23, 2003, the Reply filed July 8, 2004, the Request for Continued Examination filed September 8, 2004, the Reply mailed April 7, 2005 and the Reply mailed October 24, 2005.

In the Office Action mailed June 23, 2005, the Examiner states on page 15 that "...the sequences of ork (as stated by Ziegler) and Tie-2 (as stated in the instant invention) appear to be identical, *In re Best* (195 USPQ 430) and *In Re Fitzgerald* (205 USPQ594) apply". In column 5, lines 15-17 Ziegler states "A comparison of the amino acid sequences of ork and tie is presented in FIGS. 5a and 5b, which shows them to be distinct proteins." Ziegler then proceeds to detail the percent identity of the ork and tie amino acids sequences, which were found to be 64.5% and 47.5 respectively. At column 12 Ziegler states "...a comparison of the full length of ork and tie amino acid sequences (aligned in FIG. 5) reveals 76% identity for the cytoplasmic domains, whereas the percent identity drops to 47.5% for the full length sequences as a whole". Thus, the sequences of ork and Tie-2 are not the same. Therefore, *In re Best* (195 USPQ 430) and *In Re Fitzgerald* (205 USPQ594) do not apply.

Further, the Examiner has also rejected claims 21-27 for lack of enablement. The claims cannot be both obvious and not enabled. By rejecting claims 21-27 under 35 U.S.C. §102(a), the Examiner is implying that claims 21-27 are enabled.

Based upon the foregoing, the rejection claims 21-27 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen et al (P/N 6,160,092) in view of *In re Gulack* (703 F.2d

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1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)), *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) and Ziegler (P/N 5,447,860) is obviated and should be withdrawn.

The Examiner has maintained the rejection of claims 21-27 under 35 U.S.C. §103(a) as being unpatentable over Chen et al. (P/N 6,160,092) in view of Vikkula et al. (Cell, 1996, Volume 87, pages 1181-1190) and *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594). Applicants respectfully traverse this rejection and maintain the arguments presented in the Replies filed December 23, 2003 and January 10, 2005.

The combination of Chen et al. in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)), *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) does not suggest a method of identifying compounds that inhibit a Tie-2 protein using crystal coordinates to define the active subsites of Tie-2 and identifying a compound which binds to one or more of these active subsites in the catalytic domain. Chen et al. teaches interaction with four domains of STAT: an  $\alpha$ -helical domain, a DNA binding domain, a SH2 domain and a linking domain that links the DNA binding domain to the SH2 domain. Vikkula et al., on the other hand, discloses that mutations in the kinase domain of Tie-2 result in increased activity of Tie-2 and that an activating mutation in Tie-2 causes venous malformations. The combination of Vikkula et al. with Chen et al (P/N 6,160,092) do not teach or suggest Applicants' method of obtaining atomic coordinates comprising the catalytic domain of Tie-2 and using said atomic coordinates to obtain a compound that is an inhibitor of a Tie-2 protein.

As discussed above in the previous rejection under 35 U.S.C. § 103(a), the Examiner has also rejected claims 21-27 for lack of enablement. The claims cannot be both obvious and not enabled. By rejecting claims 21-27 under 35 U.S.C. §102(a), the Examiner is implying that claims 21-27 are enabled.

Based upon the foregoing, Applicants believe the rejection of claims 21-27 under 35 U.S.C. §103(a) as being unpatentable over Chen et al. (P/N 6,160,092) in view of Vikkula et al. (Cell, 1996, Volume 87, pages 1181-1190) and *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) is obviated and should be withdrawn.

No fees are due for the instant amendment since the total number of claims after entry of the amendments hereinabove is not more than the total number of claims that Applicants have paid for to date.

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Based upon the foregoing, Applicants believe that claims 21-27, 32 and 33 are in condition for allowance. Prompt and favorable action is earnestly solicited.

If the Examiner believes that a telephone conference would advance the condition of the instant application for allowance, Applicants invite the Examiner to call Applicants' agent at the number noted below.

Respectfully submitted,

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